Paraprotein-related Bleeding as a First Symptom of Multiple Myeloma

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Case report

Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS), Waldenström’s Macroglobulinemia (WM), Amyloidosis (AAL) or Multiple Myeloma (MM) may present both thrombotic and bleeding complications. Bleeding is commonly associated with treatment or disease related thrombocytopenia [1] while thrombosis may be related to paraneoplastic phenomena [2,3] or to treatment, as is the case with thalidomide derivatives and high dose dexamethasone [4-7]. Acquired von Willebrand disease has been described occasionally in MM and AAL but rarely induce clinically relevant bleeding [8,9]. Infrequent hemorrhagic events related to the presence of monoclonal immunoglobulins can range from skin hemorrhages to a life threatening gastrointestinal bleeding [2,3]. Specific affinity characteristics of the paraprotein with coagulation factors or platelet surface proteins have been established in some cases of severe bleeding associated to a monoclonal gammopathy [10,11].

We describe a case of a patient in which a MGUS was detected during the study of an episode of uncontrolled hematuria. A relationship between impaired coagulation parameters and serum paraprotein concentration could be established. A 72- year-old man with a prior history of diabetes, hyperuricemia and dyslipidemia, was admitted because of the acute onset of severe and uncontrolled hematuria. The initial hematology values at first admission were leukocytes 5.8 × 10⁹/L, hemoglobin 133 g/L, platelets 206 × 10⁹/L, activated Partial Thromboplastin Time (aPTT) ratio was 1.95 and Prothrombin Time (PT) ratio 1.4, fibrinogen was 426 mg/dL. After persistent bleeding, the patient required of the transfusion of six units of packed red blood cells for hemodynamic stabilization. A diagnostic procedure was performed. Ultrasound imaging of the urinary system did not find abnormalities in kidneys, bladder or prostate. A cystoscopy did not identify specific lesions but a diffuse bleeding, a random bladder biopsy was negative, an arteriography and a CT scan failed to identify anatomic lesions as a cause of bleeding. Both bladder and prostatic biopsies were negative for malignancy or amyloidosis. Hematuria was attributed to a coagulation disorder and was not controllable with fibrinogen and activated factor VII. Finally, the patient required of the urgent embolization of the hypogastric artery. Despite this procedure control of the bleeding episode was temporary and successive bleeding recurrences occurred.

The complete evaluation of hemostasis gave the following results: aPTT ratio 1.95 and TP ratio 1.44. Thrombin time and reptilase time within normal limits. Klauss quantification of fibrinogen within normal limits. The aPTT and PT did not correct after incubation for 120 min at 37°C in mixture tests. Determination of coagulation factors did not detect any deficiency, factor II was 107.7%, factor V 90%, factor VII 85.5%, factor X 131.2%, factor VIII 190.4%, factor IX 177.1%, factor XI 108.3% and factor XII 157.6% (normal limits over 70% for all factors). Results were not modified after mix with normal plasma for 120 min at 37°C. Determinations of lupus anticoagulant, anti cardiolipin and anti ß2 glycoprotein antibodies were negative. The study of von Willebrand factor was normal (von Willebrand antigen 185.3% and activity 125.4%, normal limits 60-160%). Potential platelet dysfunctions were also considered, PFA-100 was normal for both Col/ Epinephrin and COL/ADP tests (142 and 111 seconds respectively with normal limits <165" and < 118").

The patient was screened for occult autoimmune diseases, neoplasia and antibodies against clotting factors with negative results except for a protein electrophoresis that detected the presence of a monoclonal
IgG lambda monoclonal component (MC). The MC quantification by serum electrophoresis was 17.34 g/L, a bone marrow aspirate demonstrated a 10% infiltration by atypical plasma cells. Congo Red stain in bone marrow samples was negative. Calcemia, renal function and skeletal X-ray bone survey were negative. Anemia was clearly related to the bleeding episodes and consequently only a diagnosis of “smoldering” multiple myeloma could be established.

The inadequate control of bleeding and the absence of alternative explanations to justify the observed coagulation abnormalities prompted the treatment of MM, that was started with corticosteroids and melphalan (MP). Standard treatment including bortezomib was dismissed because of the risk of thrombocytopenia [1]. After six cycles of melphalan and prednisone the patient presented only a minor serological response (Figure 1), notably aPTT had partially improved and, most importantly, bleeding episodes had not recurred (Figure 1).

In the absence of bleeding and anemia, lack of symptoms or signs of active myeloma and no further improvement with MP, treatment was discontinued. During the treatment-free interval the MC concentration increased progressively and this was associated with a parallel prolongation of aPTT (Figure 1). Four months after MP discontinuation, a bone marrow aspirate reassessment revealed a 18% infiltration by atypical plasma cells, serum monoclonal component had raised to 22 g/L and aPTT had increased to 42 seconds. A decision was being made to start second line treatment with MP and bortezomib when the patient suffered an episode of phimosis and a minor surgical intervention was urgently needed. The intervention was associated with an important episode of local bleeding and extensive scrotal hematoma that could be resolved. Coagulation at that time showed a PT ratio 1.44 and a 1.36 aPTT ratio. The patient received treatment with MP and bortezomib but required the interruption of therapy after 8 cycles because of grade 2 bortezomib-related neuropathy. Again, partial improvement of paraproteinememia was associated with a partial improvement of aPTT and absence of further bleeding episodes. Again, the patient presented slow biological progression with slowly increasing levels of monoclonal component and aPTT prolongation after treatment interruption and finally presented two minor episodes of epistaxis that prompted the initiation of third line treatment with lenalidomide and dexamethasone. Once again a correlation between reduction of paraprotein and correction of aPTT has been observed despite the instauration of enoxaparin prophylaxis along with lenalidomide treatment. Figure 1 illustrates the relationship between the aPTT ratio and MC during the patient clinical evolution.

Paraproteinemias have been associated with thrombotic mechanisms such as hypofibrinolysis, increased blood viscosity, production of autoantibodies, procoagulant effects of inflammatory cytokines or resistance to activated protein C [5,6,12]. Myeloma treatment with immunomodulatory drugs is associated with thrombotic events and requires prophylactic treatment with heparin or aspirin [13]. Bleeding events in patients with plasma cell dyscrasias not related to thrombocytopenia are less frequent [2,3]. Some pathophysiological mechanisms include the interference of circulating monoclonal proteins with platelet function and coagulation factors [9-13] or acquired von Willebrand disease [8]. The detection of these abnormalities may be casual or occasional laboratory findings detected following surgery or trauma complications.
References


